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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/982,284	12/01/97	LUBON	H 030523/0141

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EXAMINER	
WILSON,M	
ART UNIT	**PAPER NUMBER**
1633	24

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	08/982,284	LUBON ET AL.	
	Examiner	Art Unit	
	Michael Wilson	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-7,11-13,15,45-47,51-65 and 67-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-7,11-13,15,45-47,51-65 and 67-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

The Examiner and Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Michael C. Wilson, Art Unit 1633.

Applicant's arguments filed 4-10-01, paper number 22, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. This action is non-final in view of the new rejections set forth below. Claims 5-7, 11-13, 15, 45-47, 51-57, 61-65 and 67-74 are pending and under consideration in the instant application.

Claim Objections

1. Claims 45 and 56 are objected to because of the following informalities:

The term "sequencesoperably" should be "sequences operably".

The term "a" should be inserted into claim 45, line 7, and claim 56, line 6, before the word "microbe."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. Claims 70 and 74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "3' urinary tract-specific regulatory sequences" (claims 70 and 74) is new matter. While the specification contemplates urinary tract-specific regulatory sequences and 3' untranslated regulatory sequences, the specification does not provide support for 3' regulatory sequences that are urinary tract-specific as newly claimed. Applicants are requested to point to support for 3' regulatory sequences that are urinary tract-specific by page and line number.

3. Claims 5-7, 11-13, 15, 45-47, 51-57, 61-65 and 67-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Regulatory sequences

The specification does not provide adequate written description for using any "regulatory sequences" to secrete an exogenous protein in the urine of a transgenic non-human animal as claimed. Lubon of record (US Patent 5,880,327, March 9, 1999) taught transgenic mice whose genomes' comprised a nucleic acid sequence encoding a protein (i.e. Factor VIII) operatively linked to the WAP promoter, obtaining expression of protein in the milk and urine of the transgenic mice and isolating the protein from the milk or urine (col. 6, lines 45-52; col. 9, line 19). Sun (WO 96/39494, Dec. 12, 1996; US Patent 5,824,543, Oct. 20, 1998, both of record)

taught transgenic mice whose genomes' comprised a sequence encoding a marker protein operatively linked to the uroplakin promoter and obtaining expression of the protein in the urine and using the bladder of the mice as a bioreactor for isolating the protein from the urine (page 8, lines 3-12; page 9, lines 15-36; page 10, line 4; paragraph bridging col. 5 and 6, col. 6, line 55, Example 2). The specification teaches making transgenic mice and pigs whose genomes' comprised a sequence encoding human protein C (HPC) operatively linked to the WAP promoter, wherein said mice and pigs expressed HPC in their urine (paragraph bridging pages 38 and 39). Therefore, the art at the time of filing taken with the teachings in the specification only support using the WAP promoter or the uroplakin promoter to direct expression of proteins to the urine as claimed.

The specification contemplates using other promoters to obtain protein expression in the urine, but do not provide any indication that the promoters have the same function or expression pattern as the WAP or uroplakin promoters. It was unpredictable at the time of filing what effect a promoter would have on the phenotype of transgenic animals (Strojek, Houdebine, Wall and Kappel all of record). Therefore, the teachings in the specification taken with the unpredictability in the art do not provide adequate written description for using any "regulatory sequences" to secrete exogenous proteins in the urine other than the WAP or uroplakin promoter.

The specification does not provide adequate written description for any "urinary tract-specific" promoters that provide expression of a protein in the urine other than the uroplakin promoter (claims 67 and 71). The uroplakin promoter causes expression in the bladder and other

urothelia (WO 96/39494, page 7, line 28). The WAP promoter is not specific to the urinary tract because it also causes expression in the mammary glands. Neither the specification or the art at the time of filing, taught regulatory sequences other than the uroplakin promoter that are urinary tract-specific. The specification does not correlate the uroplakin to any other promoters such that other promoters could drive protein expression specifically in the urinary tract. Therefore, the specification does not provide adequate written description for the genus of "urinary tract-specific" regulatory sequences other than the uroplakin promoter.

The specification does not provide adequate written description that transgenic non-human animals expressing a protein under the control of any regulatory sequences of the uromodulin gene, renin gene erythropoietin gene, an apolipoprotein E gene, an osteopontin gene, a urinary kallikrein gene, a urinary thrombomodulin gene, a uropontin gene, a nephrocalcin gene or an aquaporin gene (claims 52 and 62) or the uromodulin promoter (claims 53 and 63) would result in expression of an exogenous protein in the urine of the transgenic non-human animal. The specification and the art at the time of filing do not indicate that regulatory sequences of the uromodulin gene, renin gene erythropoietin gene, an apolipoprotein E gene, an osteopontin gene, a urinary kallikrein gene, a urinary thrombomodulin gene, a uropontin gene, a nephrocalcin gene or an aquaporin gene or the uromodulin promoter provides secretion of exogenous proteins in the urine of non-human transgenic animals. For example, Simonet (1990, J. Biol. Chem., Vol. 265, pages 10809-10812) taught transgenic mice whose genomes' comprise a transgene encoding a protein operatively linked to the apolipoprotein E promoter wherein expression of the protein

occurs in the kidney (p 28, line 3). Simonet did not teach the mice secrete the protein in their urine. Overall, the specification and the art at the time of filing do not provide any correlation between the WAP or uroplakin promoter and regulatory sequences of the uromodulin gene, renin gene erythropoietin gene, an apolipoprotein E gene, an osteopontin gene, a urinary kallikrein gene, a urinary thrombomodulin gene, a uropontin gene, a nephrocalcin gene or an aquaporin gene or the uromodulin promoter such that the regulatory sequences claimed would provide secretion of exogenous protein in the urine. Therefore, applicants were not in possession of any transgenic non-human animal that secretes exogenous protein into its urine using the regulatory sequences of the uromodulin gene, renin gene erythropoietin gene, an apolipoprotein E gene, an osteopontin gene, a urinary kallikrein gene, a urinary thrombomodulin gene, a uropontin gene, a nephrocalcin gene or an aquaporin gene or the uromodulin promoter as claimed.

The specification does not provide adequate written description for the genus of regulatory sequences that were "kidney-specific," or "bladder-specific" that provide expression of a protein in the urine as claimed (claims 68 and 72). The WAP promoter causes expression in the urinary tract and mammary glands and is not specific for the urinary tract, kidney or bladder. The uroplakin promoter causes expression in the bladder and other urothelia (WO 96/39494, page 7, line 28). Simonet (1990, J. Biol. Chem., Vol. 265, pages 10809-10812) taught transgenic mice whose genomes comprise a transgene encoding a protein operatively linked to the apolipoprotein E promoter and obtain expression of the protein in the kidney (p 28, line 3). Simonet did not teach the mice secrete the protein in their urine. While promoters may cause expression in the

kidney or bladder, neither the specification or the art at the time of filing taught regulatory sequences that are kidney-specific or bladder-specific that provide secretion of exogenous proteins in the urine. Therefore, such regulatory sequences lack written description.

The specification does not provide adequate written description of any 3' urinary tract-specific regulatory sequences that provide expression of a protein in the urine (claims 70 and 74). While the 3' region of WAP gene was used in the construct of Sympson (page 683, col. 2, line 3), Sympson did not teach the 3' region of the WAP gene was urinary-tract specific or provide expression of the protein in the urine. Neither the specification or the art at the time of filing teach a 3' urinary tract-specific regulatory sequence that provides expression of a protein in the urine. Therefore, such regulatory sequences lack written description.

In conclusion, the regulatory sequences should be limited to the WAP promoter, the uroplakin promoter or promoters that cause secretion of exogenous protein into the urine of the transgenic mammal. Claims 70 and 74 could be dependent claims wherein the transgene further comprises the 3' untranslated region of the WAP gene as taught by Sympson of record.

Proteins that degrade or detoxify organic material in the urine of transgenic non-human animals

The specification does not provide adequate written description for a transgenic non-human animal that expresses a protein that degrades food products or by-products thereof in its urine. The tissues of the transgenic non-human animal <u>are</u> food products or by-products thereof as claimed. Claims 12 and 46 specifically recite that the organic compound can be made by the

transgenic non-human animal. Therefore, the claims encompass expressing proteins in a transgenic animal that degrade tissues of the transgenic animal itself. While the prior art at the time of filing (Sympson of record) taught expressing stromelysin-1 (which degrades collagen) in transgenic mice, D'Armiento of record taught that transgenic mice expressing MMP (which also degrades collagen) do not survive (page 5734, col. 2, line 6). Collagen is considered a by-product of food. The specification does not teach expressing any enzymes that degrade food or by-products thereof in a transgenic animal. Therefore, the specification does not provide adequate written description for the genus of transgenic non-human animals that express proteins in their urine that degrade any food product or by-product thereof.

The specification does not provide adequate written description for a transgenic non-human animal that expresses proteins in its urine that such that the feces, urine, microbes or chemical pollutants are degraded/detoxified. The specification and the art at the time of filing do not teach any transgenic non-human animals that express proteins degrade/detoxify feces, urine or microbes. The specification teaches expressing human protein C (HPC) in transgenic mice and pigs (page 36). HPC is an anticoagulant (page 36, line 27) and does not degrade or detoxify anything. While the specification teaches a number of enzymes in Fig. 7 and contemplates modifying the urine and reducing the formation of antibiotic-resistant bacteria in the environment by expressing enzymes that degrade antibiotics in the urine (page 31, lines 4-13), applicants were not in possession of any transgenic non-human animals expressing proteins in their urine resulting in degrading/detoxifying feces, urine, microbes or chemical pollutants. The specification does not

teach obtaining functional enzymes in the urine or degrading/detoxifying feces, urine, microbes or chemical pollutants. Specifically, the specification does not provide adequate written description that the proteins secreted in the urine degrade herbicides, pesticides or fertilizer (claims 7 and 13). Therefore, the specification does not provide adequate written description indicting that any proteins can be secreted into the urine of a transgenic non-human animal and remain functional such that feces, urine, microbes or chemical pollutants are degraded.

4. Claims 5-7, 11-13, 15, 45-47, 51-57, 61-65 and 67-74 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic non-human mammal whose genome comprises a transgene comprising a nucleic acid sequence encoding a protein operatively linked to a promoter that causes secretion of the protein into the urine of the transgenic mammal, wherein said protein is expressed and secreted into the urine of said transgenic non-human mammal and a method of producing a protein in the urine of said non-human mammal, does not reasonably provide enablement for any transgenic non-human mammal, any regulatory sequence or any protein that degrades or detoxifies organic material that is feces, urine, a microbe, chemical pollutant or a by-product thereof, a food product or by product thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Transgenic non-human animals

The specification does not enable making any "transgenic non-human animal" as broadly claimed for reasons of record (claims 5-7, 11-13, 15, 45-47, 51-53, 56, 57, 61-63 and 67-74). Applicants argue that bird promoters have been expressed in mammals, the CRABP-1 locus from chicken and puffer fish was expressed in mice. Applicants also argue that uromodulin has been detected in amphibians and fish and the uromodulin promoter has been cloned and characterized in humans, bovines and rodents. Therefore, applicants argue that the specification provides adequate enablement for making any transgenic non-human animal that secretes exogenous protein into their urine as claimed. Applicants argument is not persuasive. While bird promoters may function in mammals, bird promoters have different functions in birds and mammals. Likewise, the mouse WAP and uroplakin promoters that cause secretion of exogenous proteins in the urine have different functions in reptiles and birds. Applicants have not provided any evidence that the mouse WAP or uroplakin promoter have the equivalent functions in mammals and birds or reptiles. Applicants have not provided any promoters that direct expression of exogenous protein in birds or reptiles. Applicants have not correlated the WAP or uroplakin promoters to bird or reptile promoters that have equivalent function in birds or reptiles. Furthermore, applicants have not provided any guidance how to make any transgenic reptiles, horses, dogs or cats (claims 55 and 65). Given the unpredictability in the art regarding how to make transgenic animals and the phenotype of transgenic animals as established in the previous office actions (Strojek, Houdebine, Wall and Kappel all of record), taken with the teachings in the specification,

it would have required one of skill in the art at the time of filing undue experimentation to determine how to make any transgenic non-human animal as broadly claimed that secreted an exogenous protein in its urine as claimed. The claims should be limited to transgenic non-human mammals as in claims 54 and 64 and the specific limitations of transgenic horses, dogs and cats should be deleted.

Regulatory sequences

The specification does not enable using any regulatory sequences as broadly claimed to obtain secretion of the exogenous protein in the urine of a transgenic non-human animal (claims 5-7, 11-13, 15, 45-47, 51, 54-57, 61, 64, 65). Lubon of record (US Patent 5,880,327, March 9, 1999) taught transgenic mice whose genomes' comprised a nucleic acid sequence encoding a protein (i.e. Factor VIII) operatively linked to the WAP promoter, obtaining expression of protein in the milk and urine of transgenic mice and isolating the protein from the milk or urine (col. 6, lines 45-52; col. 9, line 19). Sun (WO 96/39494, Dec. 12, 1996; US Patent 5,824,543, Oct. 20, 1998, both of record) taught transgenic mice whose genomes' comprised a sequence encoding a marker protein operatively linked to the uroplakin promoter and obtaining expression of the protein in the urine and using the bladder of the mice as a bioreactor for isolating the protein from the urine (page 8, lines 3-12; page 9, lines 15-36; page 10, line 4; paragraph bridging col. 5 and 6, col. 6, line 55, Example 2). Sympson of record (May 1994, J. Cell Biol., Vol. 125, 681-693) taught a transgenic mouse whose genome comprised a sequence encoding stromelysin-1 operatively linked to the WAP promoter and WAP 3' untranslated region (page 683, col. 1, first

paragraph). The WAP promoter caused expression of the protein in the milk (paragraph bridging pages 683 and 684) and inherently drives protein expression in the urine of the mice (page 28, line 24 of the instant application; Lubon, '327, col. 6, lines 45-52). The specification teaches making transgenic mice and pigs whose genomes' comprise a sequence encoding human protein C (HPC) operatively linked to the WAP promoter, wherein said mice and pigs expressed HPC in their urine (paragraph bridging pages 38 and 39). Therefore, the art at the time of filing taken with the teachings in the specification only support using the WAP or uroplakin promoter to direct expression of proteins to the urine.

The specification contemplates using other promoters to obtain protein expression in the urine, but do not correlate the function of the WAP or uroplakin promoter to any other promoters such that other promoters that drive expression of exogenous proteins in the urine of transgenic non-human mammals could be determined. Given the state of the art regarding the unpredictability of whether a promoter will have the desired phenotypic effect in transgenics as established in previous office actions (Strojek, Houdebine, Wall and Kappel all of record), taken with the art at the time of filing and the teachings in the specification, one of skill in the art at the time of filing would only have known how to obtain expression of a transgene in the urine using the WAP or uroplakin promoter. It would have required one of skill undue experimentation to determine other "regulatory sequences" that provide secretion of exogenous proteins in the urine of a transgenic non-human mammal as claimed.

The specification does not enable any "urinary tract-specific" promoters that provide expression of a protein in the urine other than the uroplakin promoter (claims 67 and 71). The uroplakin promoter causes expression in the bladder and other urothelia (WO 96/39494, page 7, line 28). The WAP promoter is not specific to the urinary tract because it also causes expression in the mammary glands. Neither the specification or the art at the time of filing taught regulatory sequences other than the uroplakin promoter that are urinary tract-specific. The specification does not correlate the uroplakin to any other promoters such that other promoters could drive protein expression specifically in the urinary tract. Given the teachings in the specification taken with the art at the time of filing, it would have required one of skill in the art at the time of filing undue experimentation to determine regulatory sequences that are "urinary tract-specific" that provide expression of a protein in the urine other than the uroplakin promoter. Therefore, the claims should be limited to the uroplakin promoter.

Specifically, the specification does not enable using regulatory sequences of the uromodulin gene, renin gene erythropoietin gene, an apolipoprotein E gene, an osteopontin gene, a urinary kallikrein gene, a urinary thrombomodulin gene, a uropontin gene, a nephrocalcin gene or an aquaporin gene (claims 52 and 62) or the uromodulin promoter (claims 53 and 63) to obtain expression of an exogenous protein in the urine of a transgenic non-human animal as claimed. The specification and the art at the time of filing does not provide any guidance indicating that regulatory sequences of the uromodulin gene, renin gene erythropoietin gene, an apolipoprotein E gene, an osteopontin gene, a urinary kallikrein gene, a urinary thrombomodulin gene, a uropontin

gene, a nephrocalcin gene or an aquaporin gene or the uromodulin promoter provides secretion of exogenous proteins in the urine of non-human transgenic animals. For example, Simonet (1990, J. Biol. Chem., Vol. 265, pages 10809-10812) taught transgenic mice whose genomes comprise a transgene encoding a protein operatively linked to the apolipoprotein E promoter and obtain expression of the protein in the kidney (p 28, line 3). Simonet does not teach the mice secrete the protein in their urine. Overall, the specification and the art at the time of filing do not provide any correlation between the WAP or uroplakin promoter and regulatory sequences of the uromodulin gene, renin gene erythropoietin gene, an apolipoprotein E gene, an osteopontin gene, a urinary kallikrein gene, a urinary thrombomodulin gene, a uropontin gene, a nephrocalcin gene or an aquaporin gene or the uromodulin promoter such that the regulatory sequences claimed would provide secretion of exogenous protein in the urine. Given the unpredictability in the art regarding whether a promoter will cause the expected phenotype in a transgenic animal as established in previous office actions (Strojek, Houdebine, Wall and Kappel all of record), taken with the art at the time of filing and the teachings in the specification, the specification does not enable making a transgenic non-human animal that secretes exogenous protein into its urine using the regulatory sequences of the uromodulin gene, renin gene erythropoietin gene, an apolipoprotein E gene, an osteopontin gene, a urinary kallikrein gene, a urinary thrombomodulin gene, a uropontin gene, a nephrocalcin gene or an aquaporin gene or the uromodulin promoter as claimed.

The specification does not enable any regulatory sequences that are "kidney-specific," or "bladder-specific" and provide expression of a protein in the urine as claimed (claims 68 and 72). The WAP promoter causes expression in the urinary tract and mammary glands and is not specific for the urinary tract, kidney or bladder. The uroplakin promoter causes expression in the bladder and other urothelia (WO 96/39494, page 7, line 28). While promoters may cause expression in the kidney or bladder, neither the specification or the art at the time of filing taught regulatory sequences that are kidney-specific or bladder-specific.

The specification does not provide teachings of any 3' urinary tract-specific regulatory sequences that provide expression of a protein in the urine (claims 70 and 74). While the 3' region of WAP gene was used in the construct of Sympson (page 683, col. 2, line 3), Sympson did not teach the 3' region of the WAP gene was urinary-tract specific or provide expression of the protein in the urine. Neither the specification or the art at the time of filing teach a 3' urinary tract-specific regulatory sequence that provides expression of a protein in the urine. It would have required one of skill in the art at the time of filing undue experimentation to determine 3' regulatory sequences that are urinary tract-specific and provide expression of a protein in the urine as claimed.

Applicants argue that other regulatory sequences are contemplated and are known to express in the urinary tract. Applicants argument is not persuasive. Secretion of the proteins into the urine is required. While promoters may direct expression in tissues of the urinary tract, such

as the kidney or bladder, the specification does not teach that any such regulatory sequence also cause secretion of the exogenous protein into the urine.

In conclusion, the regulatory sequences should be limited to the WAP promoter, the uroplakin promoter or promoters that direct expression of the exogenous protein in cells of the urinary tract of the mammal. Claims 70 and 74 could be dependent claims wherein the transgene further comprises the 3' untranslated region of the WAP gene as taught by Sympson of record.

Proteins that degrade or detoxify organic material in the urine of transgenic non-human animals

The specification does not enable expressing any protein that degrades food products or by-products thereof in the urine of a transgenic non-human animal as broadly claimed. The tissues of the transgenic non-human animal are food products or by-products thereof as claimed. Claims 12 and 46 specifically recite that the organic compound can be made by the transgenic non-human animal. Therefore, the claims encompass expressing proteins in the urine of the animal that degrade the tissue of the animal itself. While the prior art at the time of filing (Sympson of record) taught expressing stromelysin-1 (which degrades collagen) in transgenic mice, D'Armiento of record taught that transgenic mice expressing MMP (which also degrades collagen) do not survive (page 5734, col. 2, line 6). Thus, for the transgenic non-human animals or methods of using such animals to have an enabled use, the claims cannot encompass degrading the tissues of the transgenic animal and must allow the transgenic animal to survive. Support for

such an amendment should be present in the specification as originally filed and pointed to by page and line number in applicants response.

The specification does not enable expressing proteins in transgenic non-human animals that result in degrading/detoxifying the feces, urine, microbes or chemical pollutants. The specification and the art at the time of filing do not teach any transgenic non-human animals that express proteins resulting in degrading/detoxifying the feces, urine or microbes. The specification teaches expressing human protein C (HPC) in transgenic mice and pigs (page 36). HPC is an anticoagulant (page 36, line 27) and does not degrade or detoxify anything. While the specification teaches a number of enzymes in Fig. 7 and contemplates modifying the urine and reducing the formation of antibiotic-resistant bacteria in the environment by expressing enzymes that degrade antibiotics in the urine (page 31, lines 4-13), the specification does not teach obtaining transgenic non-human animals with such phenotypes. The specification does not provide adequate guidance indicating that the enzyme secreted into the urine is functional or that the enzyme degrades/detoxifies feces, urine, microbes or chemical pollutants. Specifically, the specification does not provide any guidance that the proteins secreted in the urine are able to degrade herbicides, pesticides or fertilizer (claims 7 and 13). Given the unpredictability in the art regarding the phenotype of transgenic animals (Strojek, Houdebine, Wall and Kappel all of record), taken with the art at the time of filing and the teachings in the specification, the specification does not enable expressing an enzyme in the urine of a transgenic non-human animal that degrades/detoxifies feces, urine, microbes or chemical pollutants.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 6, 11, 45, 56, 69, 70, 73 and 74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6 and 11 do not further limit claims 45 and 56 respectively because the limitation of claims 6 and 11 have been incorporated into claims 45 and 56.

Claims 69 and 70 do not further limit claim 68. Claims 69 and 70 further limit claim 67 by describing the "urinary tract-specific regulatory sequences" of claim 67 and not the "kidney-specific regulatory sequences" or "bladder-specific regulatory sequences" of claim 68.

Claims 73 and 74 do not further limit claim 72. Claims 73 and 74 further limit claim 71 by describing the "urinary tract-specific regulatory sequences" of claim 71 and not the "kidney-specific regulatory sequences" or "bladder-specific regulatory sequences" of claim 72.

Claim Rejections - 35 USC § 102

6. Claims 6, 11, 12, 45, 47, 51, 54-57, 61, 64 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Sympson of record (Sympson, May 1994, J. Cell Biol., Vol. 125, 681-693).

Sympson taught a transgenic mouse whose genome comprised a sequence encoding stromelysin-1 operatively linked to the WAP promoter and WAP 3' untranslated region (page

683, col. 1, first paragraph). The WAP promoter caused expression of the protein in the milk (paragraph bridging pages 683 and 684) and inherently results in secretion of the protein in the urine of the mice (page 28, line 24 of the instant application). Stromelysin is an enzyme that degrades collagen which is considered a by-product of food. The phrase "wherein said organic material is produced by said transgenic animal or by a different animal (claim 12) is an intended use and does not bear patentable weight in considering the art because it may not occur. Stromelysin is obtained from exthermophilic or thermophilic organisms (claims 51 and 61). A mouse is a mammal and a rodent as in claims 54, 55, 64 and 65. The teachings of Sympson are equivalent to providing the transgenic non-human animal and allowing expression in the urine as in claim 45. While claims 7 and 13 further limit the chemical pollutants in the parent claims, the claims are not limited to organic materials that are herbicides, pesticides or fertilizers. Claims 7 and 13 simply encompass proteins that degrade/detoxify organic materials that are feces, urine, microbes, herbicides, pesticides, fertilizers or by-products thereof, food products or by-products thereof. Thus, Sympson anticipates the claims.

7. Claims 6, 7, 11, 12, 13, 45-47, 51, 54-57, 61, 64, 65, 67, 69, 71, 73 are rejected under 35 U.S.C. 102(a) as being anticipated by Sun (WO 96/93494, Dec. 12, 1996) or 102(e) as being anticipated by Sun (US Patent 5,824,543, Oct. 20, 1998).

Sun taught transgenic mice whose genomes' comprised a sequence encoding β-galactosidase operatively linked to the uroplakin promoter and obtaining expression of β-galactosidase in the urine and isolating the protein from the urine (WO 96/93494 - page 8, lines 3-

12; page 9, lines 15-36; page 10, line 4; paragraph bridging col. 5 and 6, col. 6, line 55, Example 2; US Patent 5,824,543 - col. 6, lines 5 and 55). β-galactosidase is an enzyme that hydrolyses a galactoside which is considered a chemical pollutant or by-product thereof or a by-product of a food product as claimed. The phrase "wherein said organic material is produced by said transgenic animal or by a different animal (claim 12) is an intended use and does not bear patentable weight in considering the art because it may not occur. β-galactosidase is obtained from exthermophilic or thermophilic organisms (claims 51 and 61). A mouse is a mammal and a rodent as in claims 54, 55, 64 and 65. While claims 7 and 13 further limit the chemical pollutants in the parent claims, the claims are not limited to organic materials that are herbicides, pesticides or fertilizers. Claims 7 and 13 simply encompass proteins that degrade/detoxify organic materials that are feces, urine, microbes, herbicides, pesticides, fertilizers or by-products thereof, food products or by-products thereof. The uroplakin promoter is a 5' regulatory region that is specific to the urinary tract as claimed because it causes expression in the bladder and urothelia (page 7, line 28). Thus, Sun anticipates the claims as written.

Claim Rejections - 35 USC § 103

8. Claims 6, 7, 11, 12, 13, 45-47, 51, 54-57, 61, 64, 65, 67, 69, 71, 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sympson of record (Sympson, May 1994, J. Cell Biol., Vol. 125, 681-693) in view of Lubon of record (Lubon, US Patent 5,880,327, March 9, 1999), Sun of record (WO 96/39494, Dec. 12, 1996), Sun of record (US Patent 5,824,543, Oct. 20,

1998) and Wen of record (Wen et al., 1995, Molecular Reproduction and Development, Vol. 41, pages 399-406).

Sympson taught making a transgenic mouse whose genome comprised a sequence encoding stromelysin-1 operatively linked to the WAP promoter and WAP 3' untranslated region (page 683, col. 1, first paragraph) such that expression of the protein in the milk occurred (paragraph bridging pages 683 and 684) and inherently allowed secretion of the protein in the urine of the mice (page 28, line 24 of the instant application). Stromelysin is an enzyme that degrades collagen which is considered a by-product of food as claimed. Sympson did not teach isolating the protein from the urine.

However, Lubon, Sun (WO 96/39494) and Sun (US Patent 5,824,543) taught isolating exogenous protein from the urine of transgenic mice (Lubon, col. 9, line 20; WO 96/39494, page 10, line 4; US Patent 5,824,543, col. 6, line 6). It was also known at the time of filing that the WAP promoter caused expression of exogenous protein in the urine of transgenic mice (Lubon, col. 6, line 51).

Thus, it would have been obvious to one of ordinary skill in the art at the time of filing to provide the transgenic mouse expressing stromelysin under the control of the WAP promoter as taught by Sympson and isolate the protein from the urine as taught by Lubon, Sun, Sun and Wen. One of ordinary skill in the art at the time the invention was made would have been motivated to isolate proteins from the urine of a mouse expressing proteins under the control of the WAP promoter because Lubon taught that proteins under the control of the WAP promoter were

secreted in the urine, because Wen suggested isolating proteins from transgenic mice expressing proteins under the control of the WAP promoter to decrease the cost of making the protein (page 399, col. 2, first paragraph) and because Lubon, Sun and Sun suggested isolating proteins from the urine of transgenic mice.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Claims 5, 15, 52, 53, 62, 63, 68, 70, 72 and 74 appear to be free of the prior art of record because the prior art of record did not teach or suggest expressing an enzyme in Fig. 7 in the urine of a transgenic non-human animal, or using regulatory sequences of the uromodulin gene, renin gene erythropoietin gene, an apolipoprotein E gene, an osteopontin gene, a urinary kallikrein gene, a urinary thrombomodulin gene, a uropontin gene, a nephrocalcin gene or an aquaporin gene or the uromodulin promoter to obtain secretion of an exogenous protein in the urine of a transgenic non-human animal as claimed or using kidney-specific, bladder-specific or 3' urinary tract-specific regulatory sequence that cause secretion of exogenous proteins in the urine of transgenic non-human animals.

This action is non-final.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-2982.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

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